REMARKS

Claims 1-9 are currently under examination in the Application. Reconsideration is respectfully requested in view of the following remarks.

Claim Rejection Under 35 U.S.C. § 112, first paragraph (new matter)

Claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Action contends that the recitation of hyaluronic acid (HA) having molecular weight of greater than or equal to 750,000 Daltons is new matter.

Applicants respectfully traverse the rejection and submit that HA of various weights are described throughout the specification. In particular, support for HA greater than 750 kDa can be found, for example, at page 17, line 37 and page 29, line 28. HA of 750 kDa is explicitly recited at page 39, line 31 and page 40, line 16. Further, 750 kDa is used in Example 13 which describes the use of a formulation comprising HA and 5-Fluorouracil. This description of HA having a molecular weight of 750 kDa can be found at page 79, line 35, at page 80, line 4, and at page 81, Table 4. Accordingly, Applicants submit that the claims are fully supported by the specification and do not contain new matter. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Falk *et al.*, (U.S. Patent No. 5,985,850). In particular, the Action alleges that Falk *et al.* disclose injectable formulations comprising anti-cancer agents or chemotherapeutic agents combined with HA wherein the HA has a preferred molecular weight of less than 750 kDa. Further, the Action contends that Applicants' Declaration under 37 C.F.R. § 1.132 was not commensurate in scope with the claims in that no data was provided at a molecular weight of 750kD. Claims 1-9 also stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Turley *et al.* (U.S. Patent No. 6,475,795) in view of Sola *et al.* (U.S. Patent No. 6,214,860).

Specifically, the Action contends that Turley *et at.* disclose pharmaceutical compositions that comprise anti-sense nucleic acid bound to hyaluronic acid having a molecular weight of between 150 kDa and 750 kDa for treating diseases or conditions treatable using gene therapy. Turley *et al.* also allegedly disclose using hyaluronan having molecular weights of between 500 kDa and 800 kDa. The Action goes on to state that, while Turley *et al.* do not disclose non-polynucleic acid cytotoxic agents, "one cytotoxic agent can be used in place of another with the expectation of producing antineoplastic effect." Sola *et al.* generally teach cytotoxic agents such as paclitaxel, cisplatin, and camptothecin. As such, the Action asserts that it would have been obvious to the skilled artisan to combine the teachings of Turley *et al.* with the teaching of Sola *et al.* to arrive at Applicants' invention.

Applicants respectfully traverse the rejection on the following grounds.

First, in response to this rejection, Applicants submit that the claims of the present invention are directed to HA with a molecular weight greater than or equal to 750 kDa. As noted above, there is ample support for claims to HA of ≥750 kDa in the specification as filed. This molecular weight restriction, in part, distinguishes the present invention from that of Falk *et al.* who disclose only the use of HA of lower molecular weights.

Furthermore, Applicants provide herewith a further Declaration of Dr. Tracey Brown under 37 C.F.R. § 1.132 (see Exhibit 1) which includes data demonstrating that HA of molecular weight of greater ≥750 kDa is surprisingly more efficacious than HA with a molecular weight of less than 750 kDa. The experiments were designed to clearly establish the relationship between molecular weights of two different concentrations of HA with two chemotherapeutic agents, 5-Fluorouracil and methotrexate in two cell lines; a colon cancer line (LIM 1215) and breast cancer line (MDA MB 468). The six HA molecular weights were tested to cover a range from 35 kDa to 1429 kDa (*i.e.* 35, 220, 420, 750, 880 and 1429 kDa).

In summary, the data presented in the Declaration of Dr. Brown clearly demonstrate the following:

- LIM 1215 colon cancer cells treated at both low concentration (3.3 μg/ml) and high concentration (86 μg/ml) of HA demonstrate that treatment with HA of ≥750 kDa enhances the efficacy of both 5-Fluorouracil and

methotrexate as compared to lower molecular weight HA (≤420 kDa). In contrast, the lower molecular weight HA does not exert a statistically significant effect on the efficacy of the drugs as demonstrated by the IC_{50} value of the chemotherapeutic agents (Figures 1 and 2; Table 1).

- The data for the LIM 1215 colon cancer cell line with 5-Fluorouracil shows that as the concentration of HA increases from 3.3 μg/ml to 86 μg/ml (Figures 1 A and 1B, respectively), the HA of 750 and 880 kDa demonstrate equivalent efficacy to the 1429kDa HA (at the maximum concentration of 5-Fluorouracil). This suggests that there is an increase in the tertiary structure entanglement of the HA molecule which results in more efficient drug entrapment and subsequent internalisation.
- The LIM 1215 colon cancer cell line is normally resistant to methotrexate. However, when combined with higher molecular weight HA (>420kDa), the resistance is overcome where the greatest effect is seen at HA ≥750kDa (Figure 2). Resistance to methotrexate is not overcome with lower molecular weight HA. In fact, the lower molecular weight HA (35 kDa) appears to inhibit the cytotoxic activity of the methotrexate.
- In the MDA MB 468 breast cancer cell line study, the higher molecular weight HA (≥750kDa) enhances the efficacy of methotrexate while the lower molecular weight (<420kDa) does not demonstrate a significant difference as can be seen in Figure 3 and the IC_{50} values in Table 1.

These data provide factual evidence that molecular weight of HA ≥750kDa provides unusual and unexpected results compared to low molecular weight HA. Thus, Applicants submit that the skilled artisan would not have been prompted by the teachings of Falk *et al.* to use higher molecular weight HA with a reasonable expectation of success. Accordingly, the Office has not established a *prima facie* case of obviousness. As such, Applicants submit that the claimed invention is not obvious in view of Falk *et al.*

Concerning the rejection of the claims over Turley *et al.* in view of Sola *et al.*, Applicants submit that the cited references, taken either alone or for what they teach as a whole,

do not obviate the claimed invention. In particular, Applicants submit that Turley *et al.* only teach the use of HA as a targeting agent for gene therapy. Turley *et al.* provide no data or teaching that the use of high molecular weight HA (≥750 kDa) would have any effect at all on reducing or overcoming acquired or inherent cellular resistance to cytotoxic or anti-neoplastic agents as is claimed in the present invention. The general teachings of Sola *et al.* do not overcome the deficiencies of Turley *et al.* in that Sola *et al.* merely provide general teachings on cytotoxic agents with no teaching or suggestion whatsoever of the use of HA in any setting. The motivation that the Action appears to be using to combine the teachings of Turley *et al.* with the general teaching of Sola *et al.* is merely a desire to treat cancer. Clearly there is a need to solve the problems associated with cellular resistance and cancer therapy, but recognition of a need does not render obvious the achievement that meets that need. As the Federal Circuit has pointed out:

> "Recognition of a need does not render obvious the achievement that meets that need. There is an important distinction between the general motivation to cure an uncured disease [....] and the motivation to create a particular cure." *Cardiac Pacemakers Inc. v. St. Jude Medical Inc.*, 72 USPQ 2nd, 1333, 1337 (Fed. Cir. 2004).

The Federal Circuit clearly established in *in re Rouffet* that explicit teaching or implicit suggestion is required to support a *prima facie* case of obviousness. *In re Rouffet*, 47 USPQ2d 1453, 1458-59, (Fed. Cir. 1998). As discussed in *In re Rouffet*, "...the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." (emphasis added). Further, there is no motivation for the purported combination, beyond the Applicants' own teachings. To establish a prima facie case of obviousness, requires "some object teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relative teachings of the references. *In re Thrift et al.* 298 F.3d 1357 (Fed. Cir. 2002) relying on *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). While the sources of motivation may come from the nature of the problem to be solved; the teachings of the prior art; or the knowledge of persons of

ordinary skill in the art, the Federal Circuit strongly advises against hindsight reconstruction. *In re Rouffet et al.* 149 F.3d 1350 (Fed. Cir. 1998) (relying on *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991). The Court In re Rouffet notes that "virtually all inventions are combinations of old elements." *In re Rouffet et al.* 149 F.3d 1350 (Fed. Cir. 1998) (relying on *Environmental Designs, Ltd. V. Union oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983); *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1537, 1579-80 (Fed. Cir. 1983)). The Court goes on to state that:

> "[I]f identification of each claimed element in the prior art was sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit the examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *In re Rouffet et al.* 149 F.3d 1350 (Fed. Cir. 1998).
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> Such an approach would be "an illogical and inappropriate process by which to determine patentability." *In re Rouffet et al.* 149 F.3d 1350 (Fed. Cir. 1998) (relying on *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996).

Thus, it is improper to "[use] that which the inventor taught against its teacher." *In re Sang-Su Lee*, 277 F.3d 1338 (Fed. Cir. 2002) (relying on *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). "[T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine the prior art references." *In re Sang-Su Lee*, 277 F.3d 1338 (Fed. Cir. 2002) (relying on *In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir 1998); and *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984)).

To properly support a *prima facie* case of obviousness, the Examiner must show a motivation to combine the references. To this end, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the

claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet,* 47 USPQ2d 1453, 1458 (Fed. Cir. 1998). Further, when an Examiner relies on the skill in the art, the Examiner must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *Id.* As noted by the Federal Circuit, if merely "a rote invocation [of the skill in the art] could suffice to supply motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance." *Id.* Accordingly, Applicants submit that no specific reason has been given to combine the cited references. Additionally, regarding implicit teaching in the art, the Court has reiterated in a recent opinion that "... rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (emphasis in original) (Alza Corporation *v.* Mylan Laboratories, CAFC opinion 06-1019, citing Kahn, 441 F.3d at 987-988).

In the present Action, no such underpinning exists. Turely *et al.* merely utilize HA in the context of gene therapy, while Sola *et al.* merely supplies a laundry list of chemotherapeutic agents. One of ordinary skill in the art, looking to solve the problem of cellular resistance to cytotoxic or anti-neoplastic agents, clearly would not look to the gene therapy art, and likely would be wholly unaware of its contents. Further, such unexpected benefit of the combination with HA greater than or equal to 750 kDa, is simply not envisioned by the cited art.

Thus, Applicants submit that the Action has improperly relied on hindsight to combine the cited references. Applicants reiterate that there is no explicit or implicit support in any of the cited references motivating the skilled artisan to combine the references nor do the cited references provide evidence to support the Action's sweeping statement that one cytotoxic agent can be used in place of another with the expectation of producing antineoplastic effect. Accordingly, Applicants submit that the Office has not established a *prima facie* case of obviousness. Even assuming, *arguendo*, that the Office had established a *prima facie* case of obviousness, Applicants submit that the unexpected results submitted herewith rebut such a case.

In view of the above remarks and the Declaration of Dr. Tracey Brown, Applicants submit that the claimed invention is not obvious in view of Falk *et al.* or over Turley *et al.* in view of Sola *et al.* Reconsideration and withdrawal of these rejections is respectfully requested.

The claims are now believed to be in condition for allowance. A good faith effort has been made to place the application in condition for allowance. However, should any further issue require attention prior to allowance, the Examiner is requested to contact the undersigned at 206-622-4900 to resolve same.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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WTC:hh

Enclosure:
Declaration of Dr. Brown under 37 C.F.R. § 1.132
CV of Dr. Brown

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